PACKAGE LEAFLET

Package leaflet: Information for the user

Milrinone 1 mg/ml Solution for Injection and Infusion
milrinone

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist or nurse.
- If you get any side effects, talk to your doctor, or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Milrinone is and what it is used for

Milrinone is a medicine designed to increase cardiac output. The active ingredient is called milrinone. This is a substance with cardiovascular and vasodilating properties.

Milrinone is used in adults for:
Short-term treatment (up to 48 hours) of severe cardiac failure, which is not satisfactorily treatable with the usual means (cardiac glycosides, diuretics, angiotensin converting enzyme (ACE) inhibitors and vasodilators).

In children Milrinone can be used for:
- Short-term treatment (up to 35 hours) of severe cardiac insufficiency (if the heart cannot pump enough blood into the rest of the body), unless other medicines have helped,
- Short-term treatment (up to 35 hours) of acute cardiac insufficiency, e.g. After cardiac surgery, that is, when the heart has difficulty pumping the blood through the body.
During the milrinone infusion, constant monitoring of cardiac function and blood pressure must be ensured.

2. What you need to know before you use Milrinone

Do not use Milrinone
- if you are allergic to milrinone or any of the other ingredients of this medicine (listed in section 6),
- if you have severe heart valve obstruction (obstructive aortic or pulmonary valve disease),
- if your cardiac insufficiency is due to abnormal enlargement of the heart muscle cells (hypertrophic obstructive cardiomyopathy),
- if you have a circumscribed dilatation of the wall of the ventricle (ventricular aneurysm),
- if you have a severe, previously untreated fluid deficiency,
- if you have suffered an acute heart attack.

Milrinone should also not be used if your cardiac insufficiency is due to hyperthyroidism, acute myocarditis, or some form of myocardial disease (amyloid cardiomyopathy), as there is insufficient therapeutic experience.

Warnings and precautions
Talk to your doctor or nurse before using Milrinone.

- if you have been diagnosed with certain forms of cardiac arrhythmias (eg atrial flutter, atrial fibrillation, or certain other forms of arrhythmias originating in the ventricle) because milrinone injection can promote certain arrhythmias. Your physician will therefore consider whether additional antiarrhythmic treatment, dose adjustment or electrocardiographic monitoring is required.

- if you suspect that the filling pressures of the heart are lowered (eg due to previous diuretic therapy). Your physician will check the filling pressures before use and correct them if necessary.

- if you have renal disease or low blood pressure. Your physician will carry out appropriate monitoring before and during treatment to consider the treatment and dosage of milrinone injection and other medicines.

- if you have noticed a decrease in the number of platelets (thrombocytes) or red blood cells (erythrocytes) or hemoglobin concentration. Your physician will continue to use milrinone injection only with careful monitoring of the platelets, as it could lead to a further drop in these blood elements.

Cases of reactions at the infusion site have been reported. Therefore, the site where the infusion solution from the infusion cannula enters the venous blood should be carefully monitored during administration of milrinone to avoid inadvertent administration of the infusion outside the vein (extravasation).

Children and adolescents
Beyond the precautions and warnings for adults, the following should be considered for children:
Before the administration of milrinone, the physician will perform various checks, such as: the heart rate and blood pressure, and conduct some blood tests.
Milrinone will not be given if your child's heart rate and blood pressure are unstable.

Inform your physician if
- your child has renal problems,
- your child was born prematurely or has a low birth weight,
- your child has a specific heart defect called a patent ductus arteriosus: a connection between two large blood vessels (the carotid artery and the pulmonary artery) that remains open, even though it should be closed.

In these cases, your physician will decide if your child can be treated with milrinone injection.
Cardiac defects have been reported following preterm delivery.

Elderly patients
For elderly patients, no special dosage recommendations are available. Controlled pharmacokinetic studies have so far shown no age-related effect on the distribution and / or excretion of milrinone, the active ingredient of Milrinone.

Other medicines and Milrinone
Tell your doctor or pharmacist if you are using, have recently taken or might take any other medicines.

If you take diuretics at the same time as milrinone injection, your diuretic and potassium lowering effects may be exacerbated. The resulting loss of potassium can promote the occurrence of cardiac arrhythmias. The effect of milrinone can also be stronger.

Concomitant administration of milrinone injection and cardioprotective agents (eg dobutamine) may potentiate cardiopressor (positive inotropic) effects.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Currently, there is no experience with the use of milrinone in pregnant women. Animal studies did not indicate any direct or indirect harmful effects on embryonic / fetal development.
As a precautionary measure, use of milrinone during pregnancy should be avoided.

It is unknown if milrinone passes into breast milk. A risk for the newborn / child cannot be excluded. Breastfeeding should be discontinued during treatment with milrinone.

Driving and using machines
There is no impact on the driving or the ability to operate machinery.

Milrinone contains glucose
If you have been told by your doctor that you have an intolerance to some sugars, you should inform your doctor before using milrinone injection.

Milrinone contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 1 ml, that is to say essentially “sodium free”.

3. How to use Milrinone

The dosage and method of administration of Milrinone will be determined by your physician. He will generally be guided by the following dosage recommendations:

Dosage
Initial dose:
The first dose is 50 micrograms (0.05 mg) milrinone / kg body weight (BW). It is given over a period of 10 minutes. This is usually followed by a continuous maintenance infusion. (Table 1)

Maintenance dose:
In general, the continuous maintenance infusion is 0.5 micrograms of milrinone / kg BW per minute. However, it may be between 0.375 micrograms of milrinone / kg BW per minute and 0.75 micrograms of milrinone / kg BW per minute, depending on the effects on the cardiovascular system. (Table 2)

The daily dose should not exceed 1.13 mg milrinone / kg BW per day.
To administer the maintenance dose, prepare an infusion solution containing 200 micrograms of milrinone / ml. It is prepared by adding 40 ml of a carrier solution to 10 ml undiluted milrinone solution for injection. As diluents/carrier solutions, 0.9% Sodium Chloride Infusion or 5% Glucose Infusion can be used.

Table 1. Initial dose (Concentration 1 mg / ml)

Body weight of the patient (kg) compared to the amount of initial dose of milrinone									
kg	30	40	50	60	70	80	90	100	110
ml	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.5	6.0

Table 2. Maintenance dose (for continuous use)

	Dosage (microgram/ kg BW / min)	Daily dose (24 hours) * mg / kg BW
minimum dose	0.375	0.59
standard dose	0.50	0.77
maximum dose	0.75	1.13

* The "daily dose (24 hours)" (in mg/kg BW) is calculated from the respective dosage (minimum, standard, maximum dose) plus initial dose (0.05 mg/kg body weight)

Depending on the required maintenance dose (in micrograms per kg of BW per minute), the following infusion rates (in milliliters per kg of BW per hour) are obtained for the prepared infusion solution at a concentration of 200 micrograms / ml (see Table 3).
Table 3: Conversion of the maintenance dose into the corresponding infusion rate

Maintenance Dose (microgram/ kgBW per minute)	Maintenance Dose (microgram/ kgBW per hour)	Infusion rate* (milliliter/ kg BW per hour)
0.375	22.5	0.11
0.400	24.0	0.12
0.500	30.0	0.15
0.600	36.0	0.18
0.700	42.0	0.21
0.750	45.0	0.22

* calculated for an infusion solution containing 200 micrograms of milrinone per milliliter.

Use in children and adolescents
As an initial dose, the physician should administer 50 to 75 micrograms per kilogram of body weight to your child for 30 to 60 minutes.
Thereafter, the dose is 0.25 to 0.75 micrograms per kilogram of body weight per minute, depending on your child's response to treatment and the occurrence of side effects. Milrinone injection can be given up to 35 hours.

During the infusion, your child will be closely monitored: the physician will perform various checks, such as: Cardiac rhythm and blood pressure monitoring, and blood draws to monitor response to treatment and the occurrence of side effects.

Elderly patients
Based on the current state of knowledge, it is to be expected that, with normal renal function, no special dosage recommendations are necessary for this patient group.

Patients with impaired kidney function
If you have a severely impaired kidney function, the excretion of milrinone will be reduced. Therefore, depending on the extent of functional renal impairment, the maintenance dose should be reduced (see Table 4).

Table 4: Conversion of the reduced maintenance dose in renal impairment patients to the corresponding infusion rate

Creatinine clearance (ml/min/1.73 m^2)	Maintenance dose (microgram / kg BW per minute)	Maintenance dose (microgram / kg BW per hour)	Infusion rate * (milliliter / kg BW per hour)
5	0.20	12.0	0.06
10	0.23	13.8	0.07
20	0.28	16.8	0.08
30	0.33	19.8	0.10
40	0.38	22.8	0.11
50	0.43	25.8	0.13

* calculated for an infusion solution containing 200 micrograms of Milrinone per milliliter.

Method of administration
Milrinone is administered by slow intravenous injection or by intravenous infusion.
Milrinone must not be mixed with substances other than the aforementioned carrier solutions.

Furosemide is chemically incompatible with a number of substances, including milrinone. Therefore, when co-administered with furosemide or bumetanide and milrinone, different intravenous routes should be chosen or furosemide should be given in tablet form.
Milrinone should not be mixed with sodium bicarbonate infusion solutions.

Depending on the fluid requirements, infusion solutions of various concentrations can be used.
For injection, the largest possible vein should be chosen to avoid local irritation. An injection next to the corresponding blood vessel must be avoided.

Duration of treatment:
The duration of treatment should not exceed 48 hours as there are no controlled examinations for a treatment duration of more than 48 hours.
In children, the treatment duration is up to 35 hours.

If you use more Milrinone than you should
There may be a drop in blood pressure and rapid cardiac arrhythmia.
In case of overdose, your physician will stop the infusion or reduce the infusion rate and may take other appropriate measures. A specific antidote is not known.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common (may affect up to 1 in 10 people)
- mild to moderate headache,
- irregular heartbeat due to extra beats,
- tachycardia,
- cardiac arrhythmia,
- low blood pressure (hypotension).

Uncommon (may affect up to 1 in 100 people)

- reduction of platelet count,
- low potassium level,
- tremors,
- ventricular fibrillation,
- severe pain in the chest, often with tightness and shortness of breath,
- increased liver function as a result of hepatic impairment.

Rare (may affect up to 1 in 1,000 people)
- reduction in the number of red blood cells,
- reduced concentration of blood pigment.

Very rare (may affect up to 1 in 10,000 people)
- allergic (anaphylactic) shock,
- Torsades de Pointes – a serious heart rhythm problem. Signs of this include very fast, uneven or forceful heartbeat (palpitations), dizziness and loss of consciousness. You may also feel sick, have cold sweats, shortness of breath, unusual pale complexion and chest pain,
- spasmodic constriction of the bronchi,
- skin reactions such as rash.

Frequency Unknown (frequency cannot be estimated from the available data)
- renal failure due to concomitant low blood pressure,
- irritation at the infusion site.

Life-threatening cardiac arrhythmias occurred especially when irregular cardiac rhythm and / or metabolic anomalies (eg decreased potassium levels) and / or increased digitalis levels were present.

In addition to the side effects in adults, the following has been observed in children:
- bleeding into fluid-filled spaces (ventricles) that are present in the brain (intraventricular hemorrhage),
- A heart condition known as patent ductus arteriosus: a connection between two large blood vessels (the aorta and the pulmonary artery), which remains open, although it should be closed. This can result in excessive fluid load on the lungs and bleeding or damage to the intestine or intestinal tract and can be fatal.

Also, in children, there is a greater possibility of reduction of blood platelet counts than in adults. This risk increases with the duration of administration of milrinone. Cardiac arrhythmias appear to be less common in children than in adults.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Milrinone

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

Storage conditions
This medicinal product does not require special storage conditions.
Do not freeze. Store in the original package.

The product is usually clear, colourless to pale yellow solution. If there is a discoloration of the liquid or flocculation, the vial must be discarded.

Storage condition after dilution:

Chemical and physical in use stability has been demonstrated for 24 hours at 20°C to 25°C when diluted with 0.9% Sodium Chloride Infusion or 5% Glucose Infusion.

From a microbiological point of view, unless the method of dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Infusion solutions diluted as recommended with 0.9% Sodium Chloride Infusion or 5% Glucose Infusion should be freshly prepared before use.

The vials are intended for single use only. All unused products or waste materials must be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What Milrinone contains

- The active substance is Milrinone
  One vial of 10 ml solution for injection and infusion contains 10 mg of milrinone.

- The other ingredients are :
- (L)-Lactic acid, Glucose anhydrous, Water for injections, Lactic acid (for pH adjustment) and Sodium hydroxide (for pH adjustment) See section 2.

What Milrinone looks like and contents of the pack

Milrinone is a clear, colourless to pale yellow colour solution, practically free from particles. It is available as a 10 ml fill volume in a 11ml clear type-I glass vial with a 20 mm dark grey bromobutyl rubber stopper and 20 mm Orange MT flip off seal and is available in pack sizes of 1 vial and 10 vials.

Not all pack sizes may be marketed

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder

Tillomed Laboratories Limited
220 Butterfield, Great Marlings,
Luton, LU2 8DL
United Kingdom

Manufacturer[1]

Emcure Pharma UK Ltd,
Basepoint Business Centre
110 Butterfield, Great Marlings
Luton, LU2 8DL
United Kingdom

Tillomed laboratories Limited
220 Butterfield
Great Marlings
Luton, LU2 8DL
United Kingdom

This leaflet was last revised in 10/2022

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[1]Only actual manufacturer stated on printed leaflet.

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

Incompatibilities

Furosemide or bumetanide should not be administered in intravenous lines containing Milrinone Injection since precipitation occurs on admixture. Sodium Bicarbonate Intravenous infusion should not be used for dilution.
In the absence of compatibility studies, the medicinal product must note be mixed with other medicinal products.

Shelf-life:

3 years for the unopened product.

After dilution: Chemical and physical in use stability has been demonstrated for 24 hours at 20°C to 25°C when diluted with 0.9% Sodium Chloride Infusion or 5% Glucose Infusion.

From a microbiological point of view, unless the method of dilution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.'
Do not refrigerate.

Special precautions for storage:

This medicinal product does not require any special storage conditions.
Do not freeze. Store in the original package.

Instructions for dilution and administration:

Infusion solutions should be freshly prepared before use.

The following diluents may be used to prepare solutions for infusion:

- 0.9% Sodium Chloride Infusion
- 5% Glucose Infusion

Initial dose

The initial dose is 50 micrograms (0.05 mg) of milrinone/kg. It is administered slowly over a period of 10 minutes. This is usually followed by a continuous maintenance infusion.

Maintenance dose

The maintenance dose is generally 0.5 micrograms of milrinone /kg /minute. However, it may be between 0.375 micrograms of milrinone/kg/minute and 0.75 micrograms of milrinone/kg/minute.
To administer the maintenance dose, prepare an infusion solution containing 200 micrograms of milrinone/ml. It is prepared by adding 40 ml of a carrier solution to 10 ml undiluted milrinone solution for injection. The diluents/carrier solutions can be 0.9% Sodium Chloride Infusion and 5% Glucose Infusion.

Delivery rates:

Adults

The following provides a guide to maintenance infusion delivery rate based upon a solution containing milrinone 200 microgram/ml

Maintenance Dose (microgram/kg/minute)	Infusion rate* (milliliter/kg/hour)
0.375	0.11
0.400	0.12
0.500	0.15
0.600	0.18
0.700	0.21
0.750	0.22

Patients with renal impairment:

The following maintenance infusion rates are recommended using the infusion solution described above.

Creatinine clearance (ml/min/1.73 m^2),	Maintenance dose (microgram/kg /minute)	Infusion rate * (milliliter/kg/hour).
5	0.20	0.06
10	0.23	0.07
20	0.28	0.08
30	0.33	0.10
40	0.38	0.11
50	0.43	0.13

The infusion rate should be adjusted according to hemodynamic response. See section 4.2.

The vials are for single use only and should be discarded immediately after initial use.